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Alcoholic Lung Injury: Metabolic, Biochemical and Immunological Aspects

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Abstract

Chronic alcohol abuse is a systemic disorder and a risk factor for acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD). A significant amount of ingested alcohol reaches airway passages in the lungs and can be metabolized via oxidative and non-oxidative pathways. About 90% of the ingested alcohol is metabolized via hepatic alcohol dehydrogenase (ADH)-catalyzed oxidative pathway. Alcohol can also be metabolized by cytochrome P450 2E1 (CYP2E1), particularly during chronic alcohol abuse. Both the oxidative pathways, however, are associated with oxidative stress due to the formation of acetaldehyde and/or reactive oxygen species (ROS). Alcohol ingestion is also known to cause endoplasmic reticulum (ER) stress, which can be mediated by oxidative and/or non-oxidative metabolites of ethanol. An acute as well as chronic alcohol ingestions impair protective antioxidants, oxidize reduced glutathione (GSH, cellular antioxidant against ROS and oxidative stress), and suppress innate and adaptive immunity in the lungs. Oxidative stress and suppressed immunity in the lungs of chronic alcohol abusers collectively are considered to be major risk factors for infection and development of pneumonia, and such diseases as ARDS and COPD. Prior human and experimental studies attempted to identify common mechanisms by which alcohol abuse directly causes toxicity to alveolar epithelium and respiratory tract, particularly lungs. In this review, the metabolic basis of lung injury, oxidative and ER stress and immunosuppression in experimental models and alcoholic patients, as well as potential immunomodulatory therapeutic strategies for improving host defenses against alcohol-induced pulmonary infections are discussed.

1. Introduction

Chronic alcohol abuse or alcoholism cost ~$223 billion to US economy and 79,000 deaths each year (Bouchery et al., 2011). The worldwide death toll is estimated to be ~30 fold greater than that in the US (CDC, 2004; NIAAA, 2000). Approximately 10–20 million people meet the criteria of alcoholic dependence in the United States and >500 million worldwide (Grant et al., 2004; Lieber, 1995). Alcohol over consumption damages almost every organ in the body and predisposes the host to a wide range of infectious diseases such as pneumonia, acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD) (Liang et al., 2012; Pabst et al., 2011; Zhang et al., 2002a). Therefore, chronic alcohol abuse is a major health issue worldwide.

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Although ingested alcohol is mainly metabolized in the liver, a sizable amount of the dose reaches the airway passages by the bronchial circulation and is metabolized via oxidative and/or non-oxidative pathways (Manautou et al., 1992; Manautou and Carlson, 1991). Some of this alcohol may be excreted unchanged in exhaled breath. Alcohol consumption compromises systemic immunity, thereby increasing the susceptibility of the host to pulmonary infections characterized by severe symptoms, and less favorable outcomes such as ARDS and COPD ((Liang et al., 2012; Moss et al., 1996; Pabst et al., 2011). Both, ARDS and COPD in chronic alcohol abusers result in hospitalization, extensive treatment cost and significant mortalities. Therefore, alcohol abuse is a systemic disorder with specific effects on the respiratory system associated with increased incidence of infections in the lung (Gamble et al., 2006; Shellito, 1998; Vander Top et al., 2005). In this review, we summarize current understanding of ethanol metabolism in the lungs and its consequential oxidative stress and ER stress, suppression of innate and adaptive immunity of the lungs. Finally, we review therapeutic strategies used to mitigate immunosuppression and oxidative stress.

2. Metabolism of alcohol in the lungs

The majority of ingested ethanol is metabolized in the liver by cytosolic alcohol dehydrogenase (ADH) to acetaldehyde, which is further oxidized by mitochondrial aldehyde dehydrogenase (ALDH) to acetate (Lieber, 2004). Mammalian lungs can metabolize ingested ethanol by ADH followed by ALDH at rates dependent on its concentration (Bernstein, 1982; Jones, 1995; Qin and Meng, 2006; Vasiliou and Marselos, 1989; Yin et al., 1992). Ethanol can also be metabolized by microsomal cytochrome P450 2E1 (CYP2E1) and peroxisomal catalase to acetaldehyde in both the liver and in lungs (Bernstein et al., 1990; Jones, 1995; Rikans and Gonzalez, 1990; Yin et al., 1992). CYP2E1 is particularly induced during chronic alcohol abuse and is shown to be responsible for production of reactive oxygen species (Lieber, 2004). However, catalase may not be an important enzyme for ethanol oxidative metabolism due to its inhibition by ethanol (Das and Mukherjee, 2010). Mammalian lung parenchyma consist of large squamous alveolar type I epithelial cells (8% of the cells, but one of the largest cells and cover ~97% of alveolar space area), alveolar type II cells (16% of the total alveolar cells, half that of the type I pneumocyte), capillary endothelial cells (30% of the lung cells) and variable number of alveolar macrophages. Cells in the interstitial space comprised of 37% of the total cells (Matalon, 1991). Whether all cell types in the lungs metabolize ethanol is very poorly studied. Bronchial and bronchiolar epithelium, Clara cells, type II pneumocytes, and alveolar macrophages from human lung have been shown to express CYP enzymes (Hukkanen J et al., 2002). Therefore, it is likely that most of resident cells express ethanol oxidizing activity and capable of oxidizing ethanol, but specific information on the metabolism of ethanol in various cell types in the lung is largely lacking.

An alternative metabolism of ethanol is driven by fatty acid ester ethyl ester (FAEE) synthase, phospholipase D, sulfatase and glucuronidase, called as nonoxidative pathway, are also ubiquitous in the mammalian lungs (Aradottir et al., 2006; Lieber, 2004; Manautou and Carlson, 1991; Sharma et al., 1991; Zakhari, 2006). Ethyl sulfate and ethyl glucuronide are water soluble and thus rapidly excreted. On the other hand, phosphatidylethanol (PEt) and FAEEs, the products of nonoxidative metabolism of ethanol catalyzed by phospholipase D and FAEE synthase, respectively, are lipophilic and have been shown to accumulate in target organs including lungs (Aradottir et al., 2006; Aradottir et al., 2002; Bernstein et al., 1990; Kaphalia et al., 2004; Laposata and Lange, 1986; Manautou and Carlson, 1991). Although toxicity of nonoxidative metabolites of ethanol in mammalian lungs has not been investigated, mammalian lungs are well equipped for both oxidative and non-oxidative metabolism of ethanol and potential target of injury by a wide range of ethanol metabolites formed in the tissue (Fig. 1).

3. Toxicity of ethanol metabolites

Both, ADH- and CYP2E1-catalyzed oxidation of ethanol generate a reactive metabolite acetaldehyde, which readily forms adducts with proteins and causes oxidative stress (Das and Mukherjee, 2010; Jones, 1995; Zakhari, 2006). Oxidative metabolism of ethanol also increases the ratio of NADH to NAD resulting in a dysregulation of lipid metabolism (Day and Yeaman, 1994). Genetic polymorphisms and altered levels of ADH, ALDH and CYP2E1 proteins influence the consumption of and susceptibility to ethanol and is possibly involve organ-specific injuries (Yin, 1994). Once formed, acetaldehyde is rapidly absorbed through the lungs (NIAAA, 2000). Biological consequences of acetaldehyde exposure include reduced phagocytotic index of lung macrophages and degeneration of the nasal olfactory epithelium (Appelman et al., 1986; Wyatt et al., 2012). Malondialdehyde (MDA, lipid peroxidation products) and acetaldehyde (MAA)-adducted proteins formed in the lungs of mice after co-exposure of cigarette smoke and alcohol are shown to stimulate bronchial epithelial cell interleukin-8 (IL-8) production *via* the activation of proteins kinase C epsilon. Proinflammatory responses of MAA-adducted proteins *in vitro* indicates that lung surfactant proteins are biologically relevant targets for MDA and acetaldehyde adduction (Wyatt et al., 2012)

FAEEs are shown to be formed in the lungs of rats and rabbits (Manautou and Carlson, 1991). These esters are reported to be cytotoxic to cells in culture and cause pancreatic toxicity in rats administered FAEEs (Werner et al., 1997; Wu et al., 2006). However, to the best of our knowledge, the pulmonary toxicity of FAEEs in vitro or in vivo has not been investigated. Another prominent nonoxidative metabolite of ethanol reportedly present in the lungs of alcoholics is PEt (Alling et al., 2005). Therefore, an evaluation of lung toxicity of FAEEs and PEt is warranted.

4. Lungs as target of alcohol-induced oxidative stress

Oxidative stress is thought to be a central feature of alcohol over-consumption-associated tissue injury and mechanism of alcoholic lung disease and several other diseases (Halliwell, 1996; Heffner and Repine, 1989). Therefore, understanding the role of oxidative stress in the pathophysiology of alcoholic lung disease is important for devising therapeutic approaches to reverse the disease progression.

Among the organ systems, mammalian lungs are a potential target of oxidative stress resulting from chronic alcohol abuse due to their direct exposure to toxic environmental pollutants, smoke, and other particulate matter present in the ambient air. Alcohol is a well recognized systemic toxin and its oxidative metabolism to acetaldehyde generates a series of ROS and free radicals, which decreases the system's ability to detoxify the ROS generated reactive intermediates or their products (Cederbaum, 2010). ROS-induced reactions develop an imbalance between oxidant production and system's ability to detoxify the ROS generated reactive intermediates and products (Fig. 2). Reduced glutathione (GSH) and a number of antioxidant enzymes are known to reduce the systemic oxidative stress (Rahman and MacNee, 1996). Oxidation of alcohol to acetaldehyde catalyzed by ADH and/or CYP2E1 (Fig. 1) generates ROS such as superoxide anion ($O_2^{\bullet -}$), the hydroxyl ($^{\bullet}OH$), and 1-hydroxyethyl ($C_2H_5O\bullet$) radicals (Cederbaum, 2010). Such radicals can damage cellular proteins, lipids and DNA through oxidation reactions most importantly *via* peroxidation of unsaturated fatty acids. A significant amount of ethanol metabolized oxidatively in the lungs can be excreted in exhaled breath by volatilization across the alveolar-capillary membrane interface. However, local alcohol metabolism within the lung may be sufficient to exert significant oxidative stress in view of an increased ratio of oxidized to reduced GSH in lung lavage fluid, as has been reported in alcohol-fed animals and alcohol abusers (Holguin et al.,

1998; Moss et al., 2000). An altered redox state associated with increased production of ROS may damage lungs through ethanol-associated oxidation of cellular proteins, lipids and DNA. ROS and their products with cellular proteins, lipids and DNA can also act as cellular messengers in redox signaling pathways and may have far reaching adverse systemic consequences.

5. Oxidative stress and ARDS and COPD

Epidemiological studies reveal that oxidative stress is an important risk factor in the etiology of ARDS and COPD (MacNee, 2001; Moss et al., 1996). Often oxidative stress is linked with the oxidation of proteins, lipids and DNA to form oxidized proteins, lipid aldehydes and peroxides such as malondialdehyde (MDA), hexanals and 4-hydroxynenonal (4-HNE), and 8-hydroxy-deoxy-guanosine, which disrupt normal signaling events required for homeostasis and cause cell injury. Therefore, establishing a cause and effect interrelationship between toxicity and oxidative stress by assessing oxidized proteins, lipids or DNA could provide a better understanding of lung injury. However, ROS-derived reactions with endogenous biomolecules are often complex and multifaceted, resulting in the generation of secondary and tertiary reactive products and causing dimerization and polymerization between and among the radicals and adducts. These reactions are driven by significant change in redox status such as increased NADH/NAD ratio, up-regulation of NADH oxidase, and depletion of reduced GSH via its de novo synthesis and/or increased oxidation and a compromised antioxidant system (Aytacoglu et al., 2006; Polikandriotis et al., 2006; Yeh et al., 2007; Yeligar et al., 2012). Such conditions often compromise immunity and cause increased susceptibility to infection in lungs (Moss et al., 1996).

6. Antioxidants

Although the interrelationship between oxidative stress and antioxidants is not fully explored in alcoholic lung injury, reduced GSH appears to be a determining factor in human and experimental models of alcoholic lung disease (Guidot and Roman, 2002). To maintain normal physiological redox status, GSH, which is synthesized primarily in the liver, is circulated to all other organs including the lungs. Chronic alcohol ingestion depletes reduced GSH within the alveolar space by as much as 80–90%, and, consequently impairs alveolar epithelial surfactant production and barrier integrity, decreases alveolar macrophage function, and increases lung susceptibility to oxidant-mediated injury. Alcohol administration also increases glutathione turnover, a process independent of glutathione oxidation, glutathione S-transferase (GST) and glutathione peroxidase (GPX) activities. Precisely how alcohol decreases GSH levels in the lung are not well understood.

7. Alcohol abuse and endoplasmic reticulum (ER) stress in lungs

As discussed earlier alcohol abuse is a significant risk factor for ARDS and COPD. Studies in to the etiology of lung diseases like COPD and idiopathic lung fibrosis indicate a role for ER stress and unfolded protein response (UPR) pathways in their pathogenesis (Greene and McElvaney, 2010; Malhotra and Kaufman, 2007). However, scant literature exists regarding ER stress in lungs during chronic alcohol abuse.

In addition to its key role in the synthesis of proteins and in xenobiotic metabolism, another important role of ER is to correctly fold proteins and modify their tertiary and quaternary structures or direct misfolded proteins to ER associated degradation (ERAD) (Ji, 2012). Accumulation of misfolded proteins in the lumen of ER membrane causes ER stress, which activates the UPR to correctly fold unfolded proteins or remove the damaged cells by apoptosis. The UPR corrects ER stress through attenuating general protein synthesis and

translation, by increasing protein folding capacity, and by expediting the degradative process of misfolded proteins (Ji et al., 2011).

A variety of pathological conditions (oxidative stress, hypoxia or altered calcium homeostasis, glucose starvation, and infections) or chemical exposure can result in ER stress. Glucose-regulated protein (GRP) 78 and other- prosurvival ER chaperones that control stress signaling pathways in the ER membrane are activated by ER stress. When cells undergo ER stress, the UPR is activated by three resident sensors: i) protein kinase-like ER kinase (PERK); ii), inositol-requiring enzyme (IRE)-1α; and iii) activating transcription factor 6 (ATF6) (Ji, 2012). Studies of chronic inflammatory lung diseases (bronchial asthma, COPD, and cystic fibrosis) as well as data from our laboratory show increasing evidence of ER stress in ethanol-induced lung injury (Greene and McElvaney, 2010; Kaphalia and Calhoun, 2012; kaphalia et al., 2013). Earlier, Shang et al. reported activation of the ER stress pathways in the lungs of lipopolysaccharide (LPS)-treated mice (Shang et al., 2011). ER stress has been reported in the lungs of patients with familial and sporadic idiopathic pulmonary fibrosis, and produces a dysfunctional epithelial cell phenotype, facilitating fibrotic remodeling (Lawson et al., 2011). Cigarette smoke (CS) can also cause ER stress in the lungs of patients with COPD (Kelsen et al., 2008). Lung epithelial cells treated with CS extract induce ER stress and apoptosis (Tagawa et al., 2008). Impaired or inhibited proteasomal activity disrupts ERAD and causes accumulation of misfolded proteins resulting in ER stress (Chauhan et al., 2008; Kardosh et al., 2008). Therefore, ER stress appears to be a common pathological condition in various lung diseases caused by exposure to CS and inhaled environmental pollutants. Further studies to elucidate the role of ER stress and UPR in pathogenesis of alcohol abuse-related lung injury could thus lead to a better understanding of the mechanism(s) of alcoholic lung disease.

Recently, we found that primary bronchial smooth muscles cells treated with bronchial lavage fluid from severe asthmatic patients cause ER stress (Kaphalia and Calhoun, 2012). In other study, we found an up-regulation of ATF6 and PERK and/or their downstream signaling in the lungs of hepatic ADH-deficient mice fed ethanol daily for 3 months (kaphalia et al., 2013). In these studies, we found activation of XBP1, protein disulfide isomerase (PDI) and C/EBP homologous protein (CHOP) suggesting a role of ER stress in ethanol-induced lung injury. It is likely that a prolonged ER stress also contribute to the etiologies of chronic diseases. Since very little is known about ER stress in the lungs of alcohol abusers, understanding the role of ER stress in alcoholic lung disease could be useful for developing preventive measures at molecular levels.

8. Alcohol abuse and immunosuppression of respiratory tract

The respiratory tract has a sophisticated immune defense mechanism that effectively protects lungs from chemical insults, and from bacterial or viral infections. However, excess alcohol consumption suppresses the immune defense network and predisposes the respiratory tract to a range of infections (Macgregor and Loubia, 1997). Reduced innate and adaptive immunity may be an important co-morbidity in alcoholic patients, as the mortality rate alone from pneumonia is more than double in alcoholics compared with non-alcoholics (Capps and Coleman, 1923)). Because of their direct exposure to the environment, host immunity expressed in the lungs is critically important to survival, and when impaired, the lungs become potential targets of pneumonia related to bacterial and viral infections.

8.1. Innate immunity

Major components of non-specific host defense include structural airway barriers that prevent entry of pathogens into the respiratory tract, and the mucociliary lining in the surface of airways, pathogen killing mechanisms such as the production of antimicrobial

peptides, ROS, hypochlorous acid, and phagocytic defense by polymorphonuclear leukocytes (PMNs or neutrophils) and alveolar macrophages. Acute and chronic alcohol intoxication interferes with the innate response at structural and barrier levels causing leakiness between the physical barriers and mucosal organs, increased lung permeability due compromised tight junctions between the epithelial cells, and reduced cell mediated host defense mechanisms.

The cell mediated arm of innate immunity is primarily controlled by granulocytes (leukocytes or PMNs), monocytes/macrophages, dendritic cells and natural killer (NK) cells. Neutrophils are the most abundant type of PMNs in the lungs. Both chronic alcohol abuse and experimental acute and chronic alcohol ingestion inhibit pulmonary recruitment of PMNs and their functions, resulting in increased susceptibility to bacterial infections, and impaired bacterial clearance, in turn resulting in an increased incidence of lung diseases and related mortality (Zhang et al., 2002b). Alcohol-mediated effects range from the initial stages of primitive hematopoietic precursor commitment to impaired recruitment of PMNs, their adherence to endothelial cells and production of superoxide, elastase and nitric oxide synthase (Greenberg et al., 1999; Macgregor et al., 1988; Siggins et al., 2011; Stoltz et al., 1999; Vander Top et al., 2006). Alcohol ingestion interferes with differentiation and impairs phagocytic functions of alveolar macrophages (Bermudez and Young, 1991; Dannenberg, 1989; Laso et al., 2007; Lau et al., 2009; Siggins et al., 2009; Szabo et al., 2004).

The nature of immune responses and immune cell trafficking are controlled by cytokines and chemokines, respectively, although functional overlap exists. Alcohol predisposes the host to a variety of complications including an inability to produce important activating and chemotactic cytokines, and lung innate immunity by altering the expression of proinflammatory mediators. Alcohol-mediated suppression of pro-inflammatory cytokines (TNF and IL-1β) and chemokines (CINC and MIP-2) and induction of anti-inflammatory cytokines (IL-10) could be associated with an impaired host defense against infection, or an altered resolution of inflammation (Boe et al., 2003; Mandrekar et al., 1999; Standiford and Danforth, 1997; Stoltz et al., 2000; Zisman et al., 1998).

Granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF), growth factors involved in the production or differentiation of granulocytes and granulopoietic response are also significantly reduced after ethanol exposure (Basu et al., 2002; Joshi et al., 2006; Joshi et al., 2005; Zhang et al., 2005). Given the key role of neutrophils in host defense against bacterial infections, this finding is of great potential clinical relevance in alcohol-related pneumonias.

*Interferons (*IFNs) secreted from host cells in response to the presence of pathogens, particularly viruses, trigger protective immune defense and interfere with viral replications. Alcohol ingestion in humans and rodents causes reduced secretion of IFNs and contributes to an increased risk of bacterial and viral infections (Starkenburg et al., 2001; Szabo et al., 2001). The lungs of alcohol-fed rodents infected with *Klebsiella pneumoniae* showed a decreased and delayed production of IFN-γ mRNA and related proteins resulting in reduced bacterial clearance from the lungs and reduced survival of the animals (Zisman et al., 1998).

Finally, the complement system is also affected by alcohol exposure. The complements system refers to a series of proteins circulating in the blood in an inactive form, but become sequentially activated in response to the recognition of molecular components of microorganisms. Once activated, complements cover the surface of the pathogen to be recognized for the phagocytosis. Chronic alcoholic patients express abnormally low levels of complements precursors in the circulation (Bhopale et al., 2011). Further, some studies have also reported reduced activation of the complements after chronic alcohol exposure

(Bykov et al., 2007; Roychowdhury et al., 2009). Either of these abnormalities could impair complement-dependent host defense.

Therefore, a better understanding of the mechanisms by which ethanol and its metabolites regulate the expression and function of transcription factors and inflammatory mediators is needed. Many proofs of concept experiments could be evaluated using primary cell culture and animal models exposed to ethanol compared to its oxidative and non oxidative metabolites. Moreover, alcohol metabolites can also act as triggers for airway disease exacerbations especially in atopic asthmatics and in Asian populations who are known to have a reduced capacity to metabolize alcohol. Therefore, epidemiological studies in larger cohorts would improve understanding of the effects of chronic alcohol abuse and metabolites of ethanol on the complement system.

8.2. Adaptive immunity

Cell mediated adaptive immunity is another important aspect of host defense which can be impaired by alcohol and its metabolites (Fig. 3). A pathogen encounter results in dendritic cell processing and antigen presentation, which then activates and differentiates T-cells into different subtypes such as T-helper cells (Th1, 2 and 17; characterized by surface expression of CD4+) and cytotoxic T-cells, characterized by expression of CD8+ and contain powerful enzymes for inducing the death of infected cells. Finally, interplay between the B-cells and T-cells is required for optimal immune responses to counteract the invasion of most the pathogens.

Acute and chronic alcohol ingestion can interfere with antigen presentation required to activate T- and B-cells and can also markedly affect the differentiation of dendritic cells (Ness et al., 2008). A significant reduction in absolute numbers of CD4+ T lymphocytes has been reported in chronic alcoholics (Saad and Jerrells, 1991). Generally, lymphocyte proliferative responses to specific antibodies against T-cell receptors are blunted by alcohol (Domiati-Saad and Jerrells, 1993). In alcoholics, a diminished capacity of T lymphocytes to produce IFN-γ, an important cytokine that stimulates cell-mediated immunity has been reported (Chadha et al., 1991). In addition, alcohol consumption can also suppress the recruitment of CD4+ and CD8+ T lymphocytes in response to *P. carinii* infection in the lungs (Shellito and Olariu, 1998). T cells isolated from chronic alcoholics and ethanol-intoxicated animals possess a decreased response to mitogen stimulation and an impaired hypersensitivity responses (Lundy et al., 1975; Spinozzi et al., 1991). Animal studies of pulmonary tuberculosis have shown decreased lung CD4+ and CD8+ T cells and diminished proliferation in ethanol-fed mice (Mason et al., 2004).

Pulmonary host defense against bacterial pathogens is dependent on intact type-1 T-cell immunity (Greenberger et al., 1996; Moore et al., 2002). Discovery of the T-cell cytokine IL-17 is important because it serves as a link between adaptive and innate immunity upregulating chemokines and cytokines to promote neutrophilic inflammation. Animals inoculated with *K. pneumoniae* exhibit induced expression of pulmonary IL-17 within 12 h, and animals deficient in the receptor for IL-17display an increased mortality from infection with this pathogen (Ye et al., 2001). Chronic alcohol intoxication inhibits the pulmonary IL-17 response to *K. pneumoniae* infection, and shows a dose-dependent inhibition of IL-17 by ethanol after *in vitro* stimulation of T cells (Shellito et al., 2001). Therefore, induction of IL-17 cytokine can improve survival of alcohol-treated animals (Ye et al., 2001).

Despite the decreases in B cell numbers, alcoholics with liver disease have increased levels of circulating nonprotective IgA, IgM, and IgG. In contrast, bronchoalveolar lavage (BAL) fluid in patients with alcoholic liver disease exhibits reduced levels of total IgG and IgG_1 (Spinozzi et al., 1992). This defect closely correlates with the development of bacterial

pneumonia. Replacement of immunoglobulin therapy partially restores BAL Ig levels and decreases the rate of subsequent pulmonary infection, further supporting the importance of airway antibodies in host defense.

9. Approaches for treatment of alcoholic lung disease

Most therapeutic efforts directed towards alcoholic lung disease are based upon the use of direct antioxidants such as *N*-acetylcysteine (NAC) and GSH. As a precursor of cysteine needed for the synthesis of GSH, NAC acts as indirect antioxidant. Therefore, restoring GSH homeostasis in the lung by GSH replenishment or by enhancing its endogenous synthesis has therapeutic potential for treating chronic alcoholic lung disease. Such an approach can also restore antioxidant enzymes (*e.g.* glutathione reductase and superoxide dismutase).

In animals, dietary GSH supplementation is effective in maintaining GSH homeostasis, but it requires chronic GSH ingestion to prevent oxidative damage (Guidot and Brown, 2000; Guidot et al., 2000; Holguin et al., 1998). Dietary supplementation of GSH precursors can also restore both the mitochondrial and cytosolic GSH pool, as well as alveolar epithelial functions and can significantly decrease the risk of alcoholic lung injury (Guidot and Brown, 2000). Therefore, adequate GSH precursor supplementation, which might significantly decrease risk of alcoholic lung injury and possibly even pneumonia, should be a better therapeutic approach.

An association of the D/D genotype of the angiotensin converting enzyme (*ACE)* I/D polymorphism with phagocytic NADPH oxidase-mediated superoxide overproduction has been reported (Jose et al., 2009). The observation suggests that the mechanisms that control the angiotensin pathway are linked to the development of oxidative stress and potentially oxidative injury. Thus not surprisingly ACE II have been shown to significantly decrease the pulmonary complications due to alcohol abuse (Bechara et al., 2003). Therefore, ACE II inhibitors as well as AT1 receptor blockers could potentially be employed to prevent the alcoholic lung phenotype. (Fig. 4),

G-CSF enhances pulmonary clearance of bacteria from ethanol treated rats and improves their survival including the expression of adhesion molecules and phagocytosis (Stoltz et al., 1999; Zhang et al., 1999). Rats fed G-CSF (50 μg/kg) twice daily for 2 d can increase circulating PMN's within the alveolar space by 5 – 7 folds (Zhang et al., 1999). In a clinical trial of 746 patients, subcutaneous injection of G-CSF (300 μg/day) for up to 10 d increased circulating PMNs 3-fold and exhibited less complications due to ARDS and disseminated intravascular coagulation (Nelson et al., 1998). Therefore, for alcoholic lung diseases, enhancing the chemotactic signals using G-CSF can enhance recruitment of circulating PMNs in to the alveolar space.

Expressions of the GM-CSF receptor, alveolar epithelial barrier function and fluid transport are significantly reduced in rats fed ethanol (Joshi et al., 2005; Mandujano et al., 1995). These expressions can be restored by intrapulmonary administration of recombinant GM-CSF, which improves functional activities of alveolar macrophages in alcohol-fed rats and restores alveolar epithelial barrier function damaged by alcohol ingestion (Pelaez et al., 2004).

GM-CSF therapy can reduce the intensity of pulmonary *P. carinii* infection associated with enhanced alveolar macrophage TNF production in CD4 depleted mice (Paine et al., 2000). Infusion of GM-CSF at a dose of 125 μg/m2 for 72 h causes up-regulation of CD11b expression on circulating PMNs and a more frequent resolution of infection in patients (Rosenbloom et al., 2005). In a clinical trial of 1200 neutropenic patients with pneumonia, a

daily administration of GM-CSF (mean dose of 5 μg/kg daily) for a mean period of 13 d restored blood leukocyte counts (Dierdorf et al., 1997). Hematopoietic recovery was also observed in 74% of the patients with a good clinical and/or radiologic improvement. Therefore, GM-CSF therapy can be beneficial for alcoholic patients. However, higher GM-CSF daily doses (i.e., >15 μg/kg) are associated with serious side effects such as generalized inflammation and tissue injury (Arning et al., 1991).

Macrophages stimulated by IFN-γ are capable of killing over 3 dozen different pathogens (Murray, 1994). IFN-γ administered along with antibiotics produces synergistic effects in the treatment of certain pulmonary infections. Intratracheal instillation of IFN-γ or its aerosol inhalation activates alveolar macrophages that enhance the lung microbicidal activities (Beck et al., 1991; Jaffe et al., 1991). Local or systemic administration of IFN-γ alleviates alcohol-induced suppression of MIP-2 and CINC production in the lung following intrapulmonary LPS challenge. Interestingly, patients with multidrug resistant tuberculosis treated with IFN-γ rapidly clear the infection and eradicate the mycobacteria (Condos et al., 1997; Gallin et al., 1995).

Whether any particular long term therapeutic strategy will be effective for either alcoholic lung disease, ARDS or COPD cannot be predicted with certainty. Combination therapies including antibiotics will be required to treat acute and chronic lung injuries. Though dietary supplementation with GSH precursors or selective inhibition of ACE II and/or AT receptors can limit lung injury in animal models, G-CSF appears to be most attractive candidate for treating the alcoholic lung disease as well as for ARDS and COPD.

10. Conclusions

Alcoholic lung disease is a significant public health concern and understanding its mechanism should enable us to develop effective therapeutic intervention and treatment. Immunosuppression due to acute or chronic alcohol abuse appears to be a significant risk factor in the initiation and progression of ARDS and COPD. Impaired alveolar epithelial barrier functions, mucocilliary clearance and GM-CSF signaling, and increased renin angiotensin activity are the major effects of acute and chronic alcohol abuse. A dramatic depletion of reduced glutathione in the lungs of ethanol fed animals is a hallmark of the prevailing oxidative stress. Therefore, oxidative metabolism of ethanol and its associated oxidative stress have been suggested as underlying mechanisms of alcoholic lung disease. ER stress and UPR signaling in COPD and lung fibrosis have also been reported. Therefore, ER stress and oxidative stress, both associated with ethanol abuse, could be critical factors for the suppression of innate and adaptive immunity in the lungs, as is reported in ARDS and COPD. In view of the metabolic basis of alcoholic lung diseases, studies investigating the role of nonoxidative metabolites of ethanol such as FAEEs and PEt are warranted. Although not discussed in this review, discovery driven approaches such as metabolomics and proteomics could be utilized to identify molecular pathways of disease, so as to develop biomarker candidates in alcoholic lung disease. Previous therapeutic studies have largely addressed replenishing reduced GSH levels or administering GM-CSF. However, treating immunosuppressive disease related to ethanol abuse becomes even more challenging because the targets are multiple and no biomarkers are yet identified. Therefore, understanding the mechanism of immunosuppresion by ethanol oxidative metabolites in conjunction with ER stress could open new avenues to identify therapeutic targets for alcoholic lung disease.

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High lights

1. Ethanol-induced immunosuppression and alcoholic lung disease
2. Metabolic basis of alcoholic lung disease
3. Ethanol-induced oxidative stress and endoplasmic stress in lungs
4. Alcoholic lung disease and innate and adaptive immunity
5. Therapeutic approaches for alcoholic lung disease

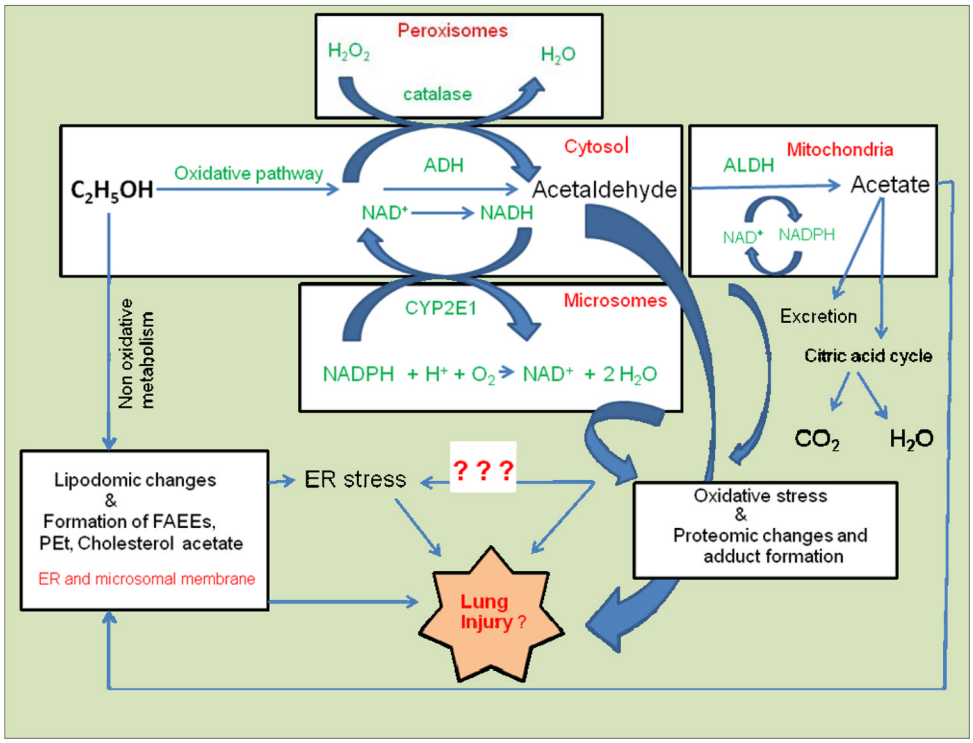

Fig. 1.

Alcohol metabolism and putative mechanism of alcoholic lung injury. The canonical pathway for ethanol metabolism is shown in the green.

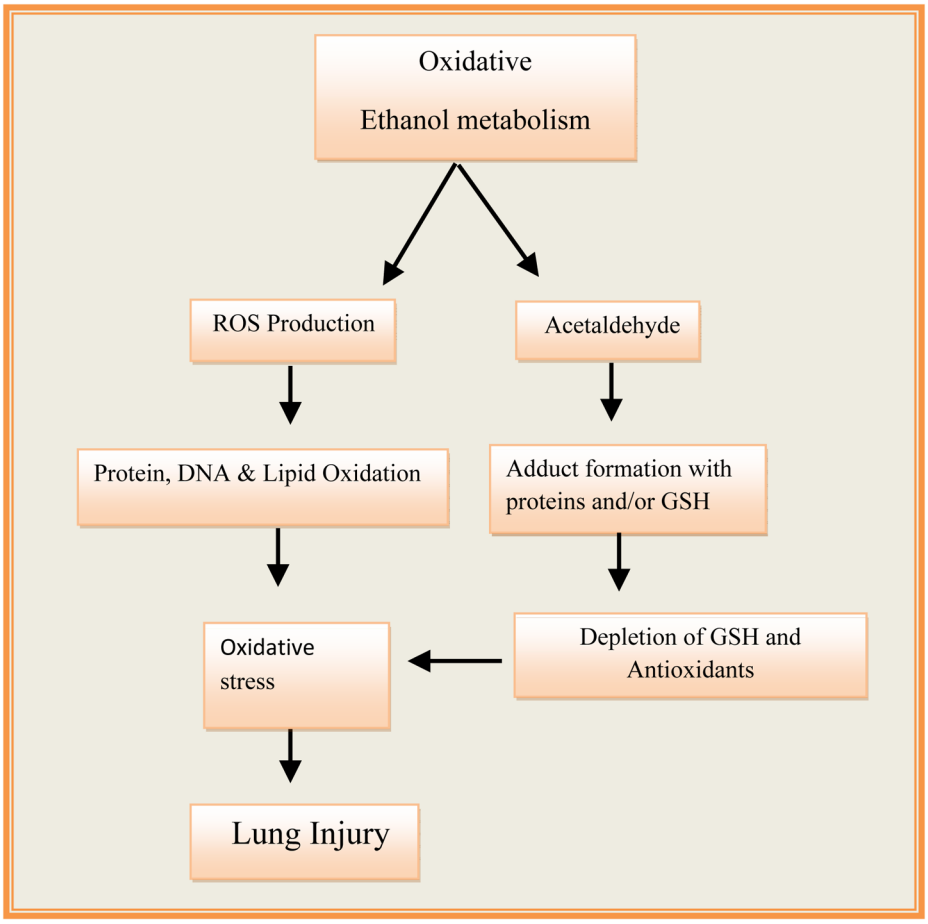

Fig. 2.
Oxidative metabolism of ethanol and related oxidative stress in alcoholic lung Injury.

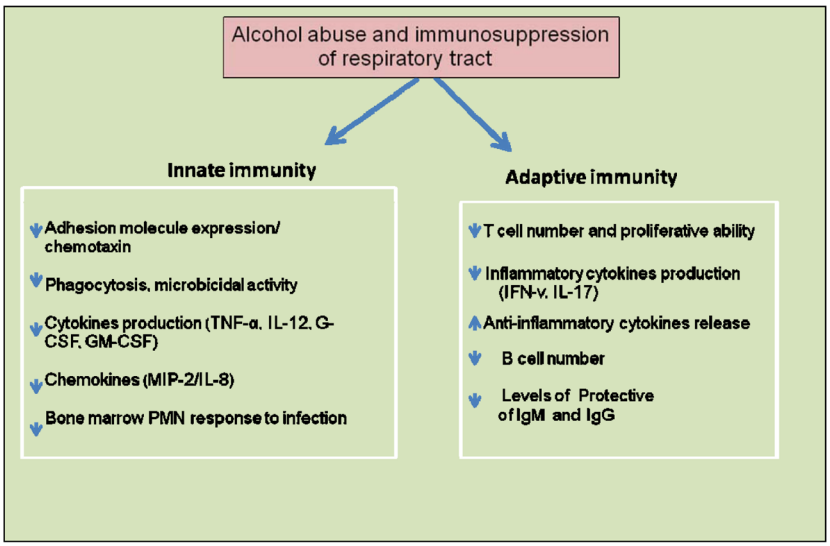

Fig. 3.

Schematic illustration by which alcohol abuse increases the risk of pulmonary infection by impairing the innate and adaptive immunity.

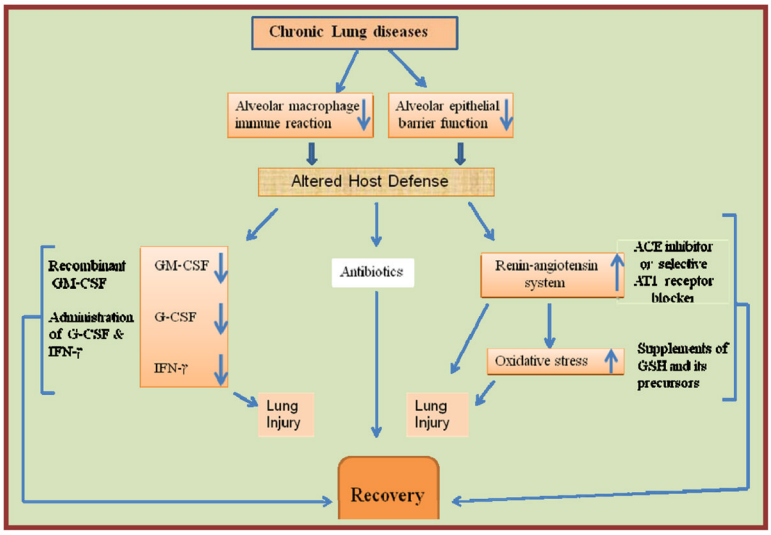

Fig. 4.
Lung injury targets in chronic alcoholic abuse and therapeutic approaches.